A NOTE

ON THE

CAUSATION AND TREATMENT OF THROMBOSIS

OCCURRING IN

CONNECTION WITH TYPHOID FEVER

BY

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We have recently, in the hope of learning something of the causes of the thrombosis which is met with in connection with typhoid fever, addressed ourselves to the task of making a series of comparative observations on the blood in (*a*) typhoid fever patients in the acute stage

of the disease, (*b*) convalescents from typhoid fever, and (*c*) in normal persons. Led by considerations which will presently appear, we measured in each case the coagulation time of the blood and its content in lime salts.

As a preliminary, a word or two may be devoted to the methods employed.

Methods.

Determination of coagulation time.—The measurement of the coagulation time was in every case undertaken at half blood-heat, or at a temperature closely approximating to this. The capillary coagulation-tubes employed were made from ordinary glass tubing drawn out in the flame. They were calibrated by introducing into the wide upper end of the tube in each case 5 c.mm. of mercury, only those tubes being selected for use where this volume of mercury formed in the capillary stem a column exactly 5 cm. in length. In carrying out this calibration, the technique described by one of us in a recent number of the 'Lancet'[1] was followed. Some minor modifications were, however, introduced. The first of these was that, blowing out the tubes in the ordinary way over filter-paper, we adjudged coagulation to be complete as soon as a definite coagulum made its appearance, irrespectively of the fact that such a clot might not be adhering firmly to the walls of the capillary tube.[2]

Another modification which we introduced was that in our later observations—and these include all those undertaken upon normal men—we made it a practice to fill in our series of coagulation-tubes from a succession of slight pricks made as they were required, instead of from one deep prick made at the outset. In this way we altogether avoid the fallaciously accelerated coagulation which

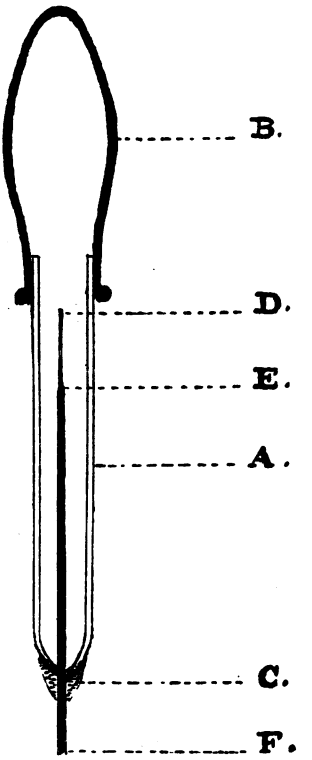
[1] July 5th, 1902.

[2] This modification in the procedure was dictated by the fact that where the coagulability of the blood is greatly reduced the coagulum may never become firm enough to block the tube.

is obtained from undue pressure on the finger and the occurrence of coagulation in the wound.

Lastly, we employed for the measurement of the standard volume of mercury, a special form of capillary

FIG. 1.



A. Wall of the glass tube which forms the barrel of the pipette.
B. Wall of the rubber teat.
C. Sealing-wax luting the lower end of the tube.
D. Filiform open extremity of the inner measuring tube.
E. Point at which the inner tube is restricted.
F. Orifice of the inner measuring tube.

pipette which takes up from the reservoir in an automatic manner the exact quantity of mercury which is required for the calibration (Fig. 1).

This automatic pipette is made as follows:—Taking in hand a capillary pipette such as might serve for the estimation of blood coagulability, we fuse it near the point in the flame of a peep-light, draw it out here into an absolutely hair-fine tube, and break this across. A 5-c.mm. volume of mercury is now, as in the calibration procedure described above, introduced. This column of mercury is driven down the capillary stem, expelling the air in front of it, until it is definitely arrested by the narrowing of the lumen. By the fact of this arrest, the hair-fine tube approves itself to be for all practical purposes closed to mercury. Noting now the level of the proximal end of the mercury column, we mark this with a file, and here snap across the capillary stem, obtaining the measuring tube we require. We now break off from the mouth-piece of our original pipette what remains of the capillary stem, and invaginate into the butt-end thus obtained our capillary measuring tube. As shown in the figure, we dispose it so that its filiform extremity may be uppermost and entirely under cover of the outer tube. Finally, with sealing-wax we make an air-tight joint between the inner and outer tube. When the pipette is to be brought into use, it is furnished with a tightly-fitting rubber teat, air is expelled from the interior, and the distal extremity (F) of the inner (capillary) tube is brought below the surface of mercury. This last, under the influence of the negative pressure, will now run up until it is arrested at the point (E) before mentioned, where the lumen of the capillary tube is too narrow to admit mercury. By the aid of this simple automatic pipette any desired number of standard volumes of mercury may be measured out in an expeditious and accurate manner.

Estimation of the content of the blood in calcium salts.—The method outlined by one of us elsewhere[1] was employed. The essential feature of the method is the mixture in capillary tubes of a succession of progressive

[1] 'Transactions of the Pathological Society of London,' 1900, p. 304, and 'Lancet,' *loc. cit.*, 1902.

dilutions of a solution of neutral oxalate of ammonium, with, in each case, an equal volume of blood. The content in calcium salts—or, more strictly, the amount of calcium salts available for the purposes of blood coagulation—is appraised by noting the minimum concentration of ammonium oxalate required to keep the blood fluid. Coagulation is judged to have been averted when no trace of clotting appears in an oxalate tube within an hour after coagulation has taken place in the blood unmixed with oxalate.

The details of the procedure are as follows :—Starting from a solution of 1 in 500 of oxalate of ammonium in 0·75 per cent. salt[1] solution, a progressive series of dilutions are made, using normal salt solution as a diluent. The dilutions which will ordinarily be required in the case of human blood will be dilutions of 1 in 800 to 1 in 2000 or over.[2]

Having made our series of dilutions, we now place a small drop of each successive dilution—measured out in an uncalibrated capillary pipette—in series upon the surface of a microscope slide. This done, we fill into the same pipette from the patient's finger, a succession of precisely similar measures of his blood. We take, of course, for each successive oxalate solution a separate volume of blood, dividing off by a series of air bubbles. The required number of measures of blood obtained, we blow these out severally with a minimum of delay into the

[1] Chemically pure reagents must be employed.

[2] For the method of making exact dilutions in an uncalibrated capillary tube see Wright, 'Lancet,' July 5th, 1902 (introductory portion of paper, Section I). By the aid of the method there described, the dilutions employed in the observations incorporated in Table I were obtained as follows :—the 1 in 800 dilution by taking up into the capillary pipette 5 volumes of the 1 in 500 dilution and 3 volumes of diluting fluid; the 1 in 1000 dilution by mixing equal volumes of the 1 in 500 solution and of normal salt solution; the 1 in 1333 solution by taking 3 volumes of the 1 in 1000 solution and 1 volume of salt solution; the 1 in 2000 and 1 in 4000 dilutions by taking up in each case 1 volume of the 1 in 500 dilution, and in the one case 3 and in the other case 7 volumes of diluting fluid.

successive drops of oxalate solution, in each case mixing. Our pipette empty, we go over the whole succession of mixtures a second time to secure that mixture shall be quite complete.

The final step in the procedure is to dispose of our oxalated bloods in such a manner as to observe their behaviour.

We may, if we please, fill them each into a separate capillary tube, and test their condition with respect to coagulation by blowing them out, after the expiration of the necessary interval, upon filter-paper.

Or—and this when practice has been acquired is more convenient—we may, dividing off as before by air bubbles, fill in, as shown in Fig. 3, the whole series of oxalated bloods into the capillary pipette which has served for the preliminary operations of measuring and mixing. If we follow this last procedure, we place the capillary pipette upright, and judge of the result after a sufficient interval, taking note whether the red blood-corpuscles have sedimented leaving a supernatant layer of plasma, or whether a filament of clot occupies the centre and a clear layer of serum has appeared along the walls of the tube.

For ward work it will be found convenient to bring to the bedside, instead of the series of watch-glasses containing the oxalate dilutions, a capillary pipette (sealed up after it has been drawn out into a hair-fine tube) filled in, as shown in Fig. 2, with a series of equal measures of the dilutions divided off by air bubbles. The pipette which does duty as a storage-tube for these dilutions will be available for the subsequent operations as described above if we take the precaution of marking off upon the capillary stem, before we empty it, a length (A—B in Fig. 2) corresponding to the particular volume of fluid which is to serve as our unit of measure.

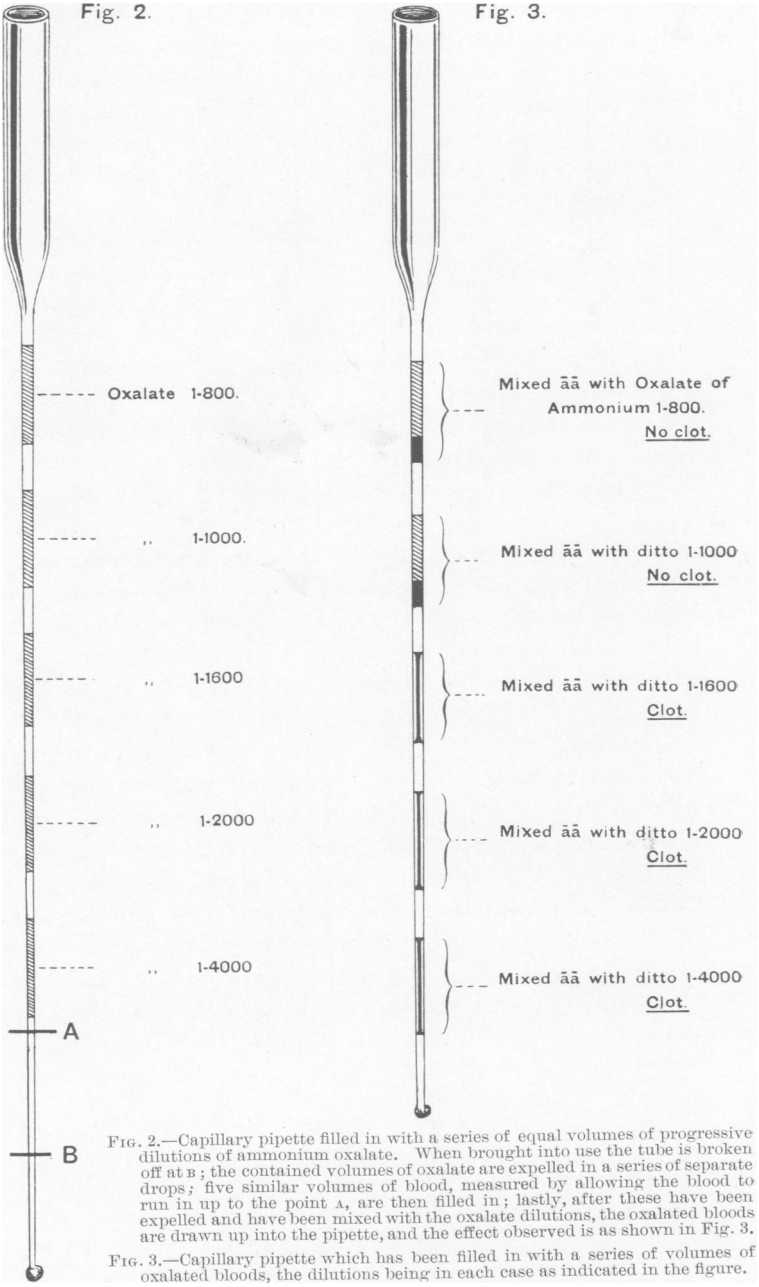


Fig. 2.—Capillary pipette filled in with a series of equal volumes of progressive dilutions of ammonium oxalate. When brought into use the tube is broken off at B; the contained volumes of oxalate are expelled in a series of separate drops; five similar volumes of blood, measured by allowing the blood to run in up to the point A, are then filled in; lastly, after these have been expelled and have been mixed with the oxalate dilutions, the oxalated bloods are drawn up into the pipette, and the effect observed is as shown in Fig. 3.

Fig. 3.—Capillary pipette which has been filled in with a series of volumes of oxalated bloods, the dilutions being in each case as indicated in the figure.

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Results of the Blood Examinations.

Results of the blood examinations undertaken on normal men.—In Table I will be found arranged in tabular form the results of a series of blood examinations undertaken upon normal men. A consideration of these brings out the fact that there is as between different individuals, and, we may add, between the blood drawn off at different times from the same individual, a considerable difference not only with respect to the blood coagulation time, but also with respect to the content in lime salts. We find that the coagulation time, determined as explained above, may, in the normal male adult, vary between three and a half minutes and eleven minutes, and the minimum strength of oxalate of ammonium solution required to avert coagulation from 1 in 800—this being altogether exceptional—to 1 in 2000.

Of importance in connection with the method of measuring the content of the blood in lime salts is the fact that it comes out clearly in Table I, and will appear more clearly in the subsequent tables, that a blood which contains less calcium salts than a control blood is not always less coagulable; nor, again, is a blood which contains more lime salts necessarily more coagulable than the control. The content of a blood in lime salts as estimated by this method is, in fact, far from being an index of its coagulability.

Results of the blood-examinations undertaken upon typhoid fever patients during the acute stage of the disease.—These results are presented in Table II. The most noteworthy feature here is the general diminution of blood coagulability.[1] Let it be observed also that the diminished coagulability furnishes an explanation of the serious hæmorrhages which may occur from comparatively small lesions in the typhoid intestine. Exceptions to the pre-

[1] It may be remarked that a comparable diminution in the coagulability of the blood supervenes upon the inoculation of large doses of "anti-typhoid vaccine."

vailing rule of the association of a condition of diminished blood coagulability with the acute stage of typhoid fever are furnished by Cases 8, 9, and 10. The first of these was a very mild case. In the last, favoured no doubt by the pneumonia and bronchitis which were marked features in this case, femoral thrombosis developed in an acute manner. The symptoms had manifested themselves only a few hours before the blood was withdrawn for examination.

Results of the blood examinations undertaken upon convalescents from typhoid fever.—The results we have obtained are incorporated in Table III. The salient feature in connection with these results is the marked increase of blood coagulability which accompanies convalescence from typhoid fever. Taking the first eight cases—all cases which were examined both during the course of the pyrexia and after the return of the temperature to the normal,—we find that the coagulation time of the blood was, on the average, four and a half times shorter in the convalescent stage than during the course of the fever (four and a half minutes as compared with twenty minutes). In Cases 1, 4, and 14, and to these may be added Case 9 from Table II, blood coagulation was abnormally rapid. In each of these cases femoral thrombosis had supervened. And these were the only cases among those examined in which it had occurred. Somewhat exceptional, though not standing entirely by itself, is Case 13. Here the diminished coagulability, which has been shown to be a feature of the acute stage of the disease, is seen to have persisted into the convalescent period. On the thirteenth day after the return of the temperature to the normal, the blood coagulation time was found to be thirty-five minutes, and this in spite of the fact that the blood contained more than the normal quantum of lime salts. On the fortieth day the coagulation time was still somewhat prolonged.

Turning our attention now more particularly to the results of the calcium salt estimations, we see that the average content of the blood in lime salts, as estimated by

the oxalate method, is, in the case of these typhoid convalescents, about twice that of the normal blood.

Therapeutical significance of the above facts.—Limiting ourselves here to the consideration of the question of the therapeutics of thrombosis, we may, as a preliminary to setting forth the treatment we adopted, direct attention to a fundamental point in connection with intra-vascular coagulation. Arguing from what occurs *in vitro*, we might expect that in the case where a thrombus forms in a vein, the patency of the vessel would be rapidly restored by the contraction of the clot. We do, as a matter of fact, see this happening in connection with the intra-vascular thrombosis, which supervenes upon the injection of cell-nucleo-albumens (Wooldridge's "tissue fibrinogens"). If the animals survive this thrombosis for a few hours, we find the thrombus, which previously blocked the vessel, represented by a mere filament of clot. But the conditions are here quite special. As pointed out by Wooldridge, there supervenes here upon the "positive phase" of increased coagulability which culminates in the thrombosis a "negative phase" of diminished or abolished blood coagulability. By reason of the supervention of this "negative phase," the thrombus, when once formed, does not receive any further accretions of fibrin from the circulating blood.

Quite different are the circumstances when the blood maintains its original coagulability. Here, as soon as any blood-flow is re-established past the clot, additional fibrin will be deposited, and the thrombus will grow larger and firmer until at last it is converted into a solid plug of "white blood-clot," which definitely blocks the vessel. Probably in this way are sown the seeds of the permanent trouble so often seen after typhoid thrombosis, and we may add after phlegmasia alba dolens.

Recognising the practical importance of the after-deposition of fibrin upon the thrombus, the coagulation time of the patient's blood subsequent to the development of thrombosis is a matter of concern. A reference to Table III will show that in each of the cases of throm-

bosis—and these were examined respectively eight, twenty-one, and forty-five days after the date of the original thrombosis—the blood was found to be abnormally coagulable. The blood conditions were thus, at these dates, still favourable to a deposition of fibrin upon the clot.

We proposed to ourselves, both in these cases and in the case of acute thrombosis, referred to above as having occurred during the pyrexial stage of the fever, to place an obstacle in the way of this deposition of fibrin by diminishing the patient's blood coagulability. With this view we administered a decalcifying agent[1]—citric acid.

In Table IV will be found details of the amount of citric acid given, and of the effect of the treatment. It will be seen that in each of the seven patients observed the exhibition of citric acid was followed by a decalcification of the blood and a corresponding diminution of its coagulability. Hand-in-hand with the blood changes went, in the case of acute thrombosis already referred to, a rapid alleviation of the symptoms.

Inferences with regard to the causation of the thrombosis which occurs in connection with typhoid fever.—Turning, in conclusion, to the problem as to what is the cause of the thrombosis so frequently seen in connection with typhoid fever, and scrutinising the results of the blood examinations to see whether they shed any light upon this problem, our attention fastens on the fact that the quantum of lime salts in the blood of the typhoid convalescents examined was greatly in excess of that in the normal blood. This fact suggests that the increased coagulability during the convalescent stage may be dependent upon an excess of lime salts. Evidence pointing in the same direction is afforded by the circumstance that the blood coagulation times of our typhoid patients, after the con-

[1] For previous experiments on the effect of the exhibition of decalcifying agents (citric acid and soap) see Wright, 'British Medical Journal,' July 14th, 1894, and 'Transactions of the Pathological Society,' vol. li, part iii, 1900.

tent of their blood in lime salts had been brought within the limits of the normal, were (as is brought out by a comparative study of Tables IV and I) longer than those of normal bloods, instead of being shorter, as we should expect them to be if the increased coagulability were dependent upon an increase in the albuminous elements which enter into the composition of the fibrin.

When we consider whence the excess of lime salts which appears to be present in the blood of the typhoid convalescent can be derived, we recognise that it must be derived from the milk which, for the most part, constitutes the exclusive dietary of the patient. Cow's milk, be it noted, contains 1 part in 600 of CaO as compared with 1 part in 800 contained in lime water.[1]

If we have, in the milk dietary of the typhoid patient, the key to the problem of the frequency of thrombosis in the period of convalescence, we have probably obtained a clue also to the resolution of certain other problems; in particular the problem of the frequently beneficial effect of a milk dietary on "serous hæmorrhage" from the kidney, and the comparative rarity of thrombosis after acute fevers such as Malta fever, where a milk dietary is not imposed upon the patient.

We obtain at the same time indications for the prophylaxis and after-treatment of thrombosis, both when it occurs in connection with typhoid fever and when it occurs in connection with other diseases. The remedial measure which would seem indicated is the exhibition of citric acid. The same treatment, initiated as soon as the danger of intestinal hæmorrhage has been surmounted, would be appropriate for prophylaxis of typhoid thrombosis.

Or, as an alternative, we might, with a view to restricting the intake of lime salts, appropriately undertake a partial decalcification of the milk. One of us has already pointed out[2] that a partial decalcification such as is here con-

[1] In the case of our patients milk formed a very important element of their dietary for a period of many weeks after convalescence.

[2] Wright, 'Lancet,' July 22nd, 1893.

templated is advisable also from the point of view of rendering the milk more easily digestible, and of preventing constipation. The partial decalcification in question can be readily effected by adding to the milk 0·25 to 0·5 per cent. of citrate of soda (20 to 40 grains per pint).

TABLE I.—*Normal Men.*

Showing the blood coagulation time and the strengths of neutral ammonium oxalate solution which respectively averted and failed to avert coagulation when added to the blood in equal volume.

Initials of the persons who furnished the blood.	Coagulation time, estimated in capillary tubes of the new standard size at 18·5° C. (half blood-heat).	Concentration of the solutions of oxalate of ammonium solution which were mixed with the blood for the purpose of estimating its content in calcium salts.					
		1 in 800 (5 in 4000).	1 in 1000 (4 in 4000).	1 in 1333 (3 in 4000).	1 in 1600 (2·5 in 4000).	1 in 2000 (2 in 4000).	1 in 4000 (1 in 4000).
A. W.	6′ 30″	0	0	Trace	—	Clot	Clot
C. K.	7′ 10″	0	0	,,	—	,,	,,
R. C.	11′	0	0	Clot	—	,,	,,
G. E. V.	8′ 15″	0	0	,,	—	,,	,,
A. A.	7′ 30″	0	0	0	—	,,	,,
S. D.	5′ 45″	0	0	0	—	,,	,,
R. W.	6′ 10″	0	0	0	—	,,	,,
J. S.	9′ 15″	0	0	0	—	,,	,,
J. R.	8′ 10″	0	0	0	—	,,	,,
B. S.	10′ 15″	0	0	0	—	,,	,,
R. E. S.	9′	0	0	Trace	—	,,	,,
J. B.	10′ 10″	0	0	Clot	—	,,	,,
O. N.	8′	0	0	,,	—	,,	,,
W. B. L.	4′	0	0	Trace	—	,,	,,
G. E. V.	8′ 45″	0	0	0	0	,,	,,
N. M.	8′	0	Clot	Clot	Clot	,,	,,
N. C.	6′	0	0	0	0	,,	,,
J. M.	8′	0	0	0	Clot	,,	,,
C. P.	9′	0	0	Trace	,,	,,	,,
D. B.	6′ 30″	0	0	Clot	,,	,,	,,
W. R.[1]	8′	Clot	Clot	,,	,,	,,	,,
P. L.	7′	0	0	0	,,	,,	,,
T. Y.	8′ 20″	0	0	0	,,	,,	,,
M. M.[2]	6′	0	0	0	,,	,,	,,
M. M.[2]	3′ 30″	Clot	Clot	Clot	,,	,,	,,
W. R.[1]	6′ 30″	,,	,,	,,	,,	,,	,,
T. H.	6′	0	0	,,	,,	,,	,,

[1] The observations here in question were made at an interval of a few days.

[2] The observations here in question were made at an interval of about forty-eight hours.

TABLE II.—*Typhoid Patients in the Acute Stage.*

Showing the results of the blood examinations undertaken on typhoid fever patients (soldiers) in the acute stage of the disease.

Serial number.	Notes with regard to the clinical features of the case and the stage of the disease at the date of the observation.	Coagulation time.	Estimation of content of blood in calcium salts, *i. e.* concentration of oxalate of ammonium solution, which (added to the blood in equal volume) just sufficed to avert coagulation.
Case 1	Fourth week of pyrexia; case has been complicated by epistaxis and pleural effusion	30′	1 in 2000
Case 2	Beginning of fourth week of pyrexia	12′	1 in 750
Case 3	Eleventh day of relapse	15′	1 in 900
Case 4	About seventeenth day of pyrexia	22′	1 in 2000
Case 5	Uncomplicated case; temperature falling by lysis	15′	1 in 2500
Case 6	About fourteenth day of pyrexia	30′	1 in 1500
Case 7	Tenth day of relapse	30′	1 in 900
Case 8	Tenth day; very mild case	5′	1 in 900
Case 9	Fourth week of pyrexia; complicated by pneumonia, capillary bronchitis, and on day of observation by acute femoral thrombosis	1′ 45″	1 in 700
Case 10	Uncomplicated case; beginning of fourth week	5′	1 in 600
Case 11	Fourth day of relapse; history of hæmorrhages in primary attack	17′	1 in 1000
Case 12	Beginning of fourth week of pyrexia; much bronchitis	16′	1 in 900

TABLE III.

Showing the results of the blood examinations undertaken on soldiers convalescent from typhoid fever.

Serial number.	Notes with regard to the clinical features of the case and the stage of convalescence at which the patient had arrived at the date of the observation.	Coagulation time (followed in brackets by the coagulation time as previously determined in the stage of pyrexia).	Estimation of content of the blood in calcium salts, *i. e.* concentration of ammonium oxalate solution, which (added to the blood in equal volume) just sufficed to avert coagulation.
Case 1	Fourteenth day of apyrexia; three weeks subsequent to development of slight femoral thrombosis	2′ [*30′*]	1 in 900
Case 2	Twenty-fourth day of apyrexia	4′ 15″ [*12′*]	1 in 700
Case 3	First day of apyrexia	4′ 30″ [*15′*]	1 in 1500
Case 4	Seventh week of apyrexia; eight days after development of slight femoral thrombosis	1′ 10″ [*22′*]	1 in 700
Case 5	Twentieth day of apyrexia; after taking citric acid 2·5 grammes t. i. d. for six days	4′ [*15′*]	1 in 1500
Case 6	Second day of apyrexia	4′ [*30′*]	1 in 700
Case 7	Seventh day of apyrexia	10′ [*30′*]	1 in 1500
Case 8	First day of apyrexia	5′ [*5′*]	—
Case 13	Thirteenth day of apyrexia	35′	1 in 700
	Fortieth day of apyrexia	11′	1 in 900
Case 14	Fifty-fifth day of apyrexia; forty-fifth day after development of thrombosis	1′ 30″	1 in 700
Case 15	Third week of apyrexia	3′ 15″	1 in 700
Case 16	Fourteenth week of apyrexia	9′	1 in 550
Case 17	Third week of apyrexia	9′ 30″	1 in 700
Case 18	Third week of apyrexia	10′	1 in 800
Case 19	First day of apyrexia	7′	1 in 700
Case 20	Fifth day of apyrexia	4′ 30″	—
Case 21	Fifth day of apyrexia	5′	—
Case 22	Tenth day of apyrexia	9′ 30″	—

TABLE IV.

Exhibiting the effect of the decalcifying treatment adopted in the case of typhoid convalescents possessing an unduly coagulable blood.

Initials of patient.	Date of observation.	Notes with regard to dietary and treatment.	Notes with regard to clinical symptoms at date of observation.	Blood coagulation time in standard tubes, at 18·5° C.	Estimation of content of blood in calcium salts. Concentration of ammonium oxalate solution which, when added in equal volume to the blood, respectively averted and failed to avert coagulation.				
					$\frac{1}{600}$	$\frac{1}{800}$	$\frac{1}{1000}$	$\frac{1}{2000}$	$\frac{1}{3000}$
J. B.	8.7.02	Milk diet	Typhoid fever, fourth week, complicated by pneumonia and capillary bronchitis; today acute development of femoral thrombosis	1′ 45″	0	0	Clot	Clot	Clot
	10.7.02	Ditto + citric acid 4 grms. (ʒj) t. i. d. (since 8.7.02)	Pain and swelling in limb less; fever continues	6′					
	11.7.02	Ditto	No change	7′ 30″	0	0	,,	,,	,,
	13.7.02	Ditto	Œdema and pain in the limb have quite disappeared; fever continues	7′ 15″	0	0	,,	,,	,,
	14.7.02	Ditto	No change	5′ 45″	0	0	0	,,	,,
B. D.	7.7.02	Convalescent diet, including milk (circ. 2 pints)	Fourteenth day of apyrexia; twenty-second day after slight thrombosis	2′	0	0	Clot	Clot	Clot
	14.7.02	Ditto + citric acid 2·5 grms. (circ. 36 grs.) t. i. d. (since 12.7.02)	—	3′ 45″	0	0	Trace	,,	,,
	19.7.02	Ditto	—	Over 15′	0	0	0	,,	,,

C. D.	8.7.02	Convalescent diet, including milk (circ. 2 pints)	Fifty-fifth day of apyrexia; forty-fifth day after thrombosis	1′ 30″	0	Clot	Clot	Clot	Clot
	14.7.02	Ditto + citric acid 2·5 grms. t. i. d. (since 12.7.02)	—	3′ 15″	0	Trace	,,	,,	,,
	19.7.02	Ditto	—	10′	0	0	,,	,,	,,
J. A.	8.7.02	Convalescent diet, including milk (circ. 2 pints)	Seventh week of apyrexia; seventh day after thrombosis	1′ 10″	0	Clot	Clot	Clot	Clot
	15.7.02	Ditto + 2·5 grms. of citric acid t. i. d. (since 12.7.02)	—	5′	Trace	,,	,,	,,	,,
	20.7.02	Ditto	—	Over 20′	0	0	,,	,,	,,
D. R.	8.7.02	Convalescent diet, including milk (circ. 2 pints)	Third week of apyrexia	3′ 15″	0	Clot	Clot	Clot	Clot
	15.7.02	Ditto + 2·5 grms. of citric acid t. i. d. (since 12.7.02)	—	4′ 45″	0	0	Trace	,,	,,
	19.7.02	Ditto	—	13′ 30″	0	0	Clot	,,	,,
R. D.	8.7.02	Convalescent diet, including milk (circ. 2 pints)	Fourteenth day of apyrexia	9′	Clot	Clot	Clot	Clot	Clot
	15.7.02	Ditto + citric acid 2·5 grms. t. i. d. (since 12.7.02)	—	9′ 30″	0	0	0	,,	,,
	19.7.02	Ditto	—	10′	0	0	Clot	,,	,,
F. D.	8.7.02	Convalescent diet, including milk (circ. 2 pints)	Third week of apyrexia	9′ 30″	0	Clot	Clot	Clot	Clot
	16.7.02	Ditto + citric acid 2·5 grms. t. i. d. (since 12.7.02)	—	Over 13′ 30″	0	0	,,	,,	,,
	19.7.02	Ditto	—	Over 30′	0	0	0	,,	,,

DISCUSSION

Dr. WILLIAM HUNTER thought the explanation given of the thrombosis from the increase of lime salts in the blood was instructive. The deductions in regard to the amount of lime salts were also instructive. The administration of sodium citrate had been found practically useful in the treatment of febrile cases in the London Fever Hospital. It was well known that typhoid patients were too largely fed with milk. He asked if Professor Wright's observations could be extended to diphtheria treated by antitoxin.

Dr. H. D. ROLLESTON asked if Professor Wright considered that the phlebitis and secondary thrombosis were both due to increased coagulability of the blood. It was generally thought that the phlebitis depended on an infection of the vein wall with typhoid bacilli. He pointed out that the cases of typhoid in South Africa showed an excess of cases of thrombosis. This had been ascribed to the use of tinned meats by the late Dr. Washbourn, and to the over-exertion of the lower limbs in the constant trekking of the troops, by himself; but it was possible that tinned milk might contain an excess of lime salts, and thus further, on Professor Wright's theory, the tendency to coagulation.

Dr. NEWTON PITT also pointed out that micro-organisms had been found in the thrombi in typhoid cases, and also with phthisis. It was, however, a question whether they appeared before or after the thrombus had formed. He asked if the total excess of lime salts found in the blood of patients with thrombosis in typhoid did not exceed that supplied by the milk. Also in regard to thrombosis in other diseases—especially in influenza—in which no excess of milk was taken, how could this be ascribed to an excess of lime salts? Similarly in gouty thrombosis the milk theory would not hold. He asked also how Professor Wright would explain the absence of thrombosis in milk-fed infants. A point had been put forward in the paper, however, of extreme practical value.

Dr. CYRIL OGLE suggested that the treatment by citric acid might be attended by some danger of embolism if it were begun after the onset of thrombosis in a vein, since its effect apparently would be to prevent complete occlusion and arrest of blood-stream in the vessel, on the wall of which a parietal thrombus had already formed. He asked whether, in the cases quoted, any lung symptoms had developed, such as a slight attack of pleurisy. Such symptoms were often misinterpreted, and their origin in small venous embolisms overlooked.

Professor WRIGHT, in reply, said that he had not made any bacteriological observations on the thrombosed vessels; he had not had the opportunity. He thought bacteria might be one factor in the process. He was far from wishing to maintain that lime salts were the only factor in causing thrombosis; his position was that when there was an excess of lime salts in the blood a slight increase of its albuminous substance, or of the leucocytes, might occasion a thrombosis. In regard to children, it was not known whether they absorbed the whole of the lime that was taken in the milk, and, moreover, blood coagulability was low in children. As to influenza, other causes of blood coagulation, no doubt, came into play, such, possibly, as an excess of leucocytes. But the ordinary causes of excessive clotting were absent in typhoid fever; hence he maintained that in this disease the excess of lime salts was probably the principal factor. He had seen no evidence of embolism after the administration of citrate of soda; nor did he see reason to anticipate it. He considered that the large number of cases of thrombosis in South Africa might be due to the use of condensed milk, as, of course, bulk for bulk, it must be richer in lime salts than fresh milk. The amount of milk in the diet would far more than suffice to account for the surplus of lime circulating in the blood.